Histopathology of Early Myocardial Infarcts

A New Approach

Bernard Bouchardy, MD and Guido Majno, MD

The histopathology of human myocardial infarcts is reviewed in a series of 46 cases ranging from sudden death to a clinical age of 3 days. A set of histopathologic features is described whereby the diagnosis of acute myocardial infarction can be made, even in cases of sudden death, on routine sections and even after considerable autolysis. This is primarily a stretching and waviness of the myocardial fibers, especially at the border of the infarcted area. Its mechanism is probably twofold: the rythmical pull exerted by the normal myocardium against the infarcted paralyzed area and the outward bulging of this area at every systole. On the basis of human material alone, it may be inferred that this pattern develops very rapidly: surely less than 1 hour and perhaps a few minutes after the local circulation has failed (Am J Pathol 74:301–330, 1974).

ACUTE MYOCARDIAL INFARCTION kills about 500,000 people every year in the United States alone; to 25% of these, death comes abruptly and unexpectedly, usually within 1 hour of the first clinical symptoms.[1] Often there is no time to establish a firm clinical diagnosis; the last chance to find out what really happened is therefore *post mortem*.

Stated in terms of general pathology, the problem is to recognize an infarct that has occurred within a very short time, of the order of 1 hour. This requirement is difficult to meet because many types of cells can survive a period of ischemia considerably longer than 1 hour; hence the problem is not only that of recognizing early signs of cell death (already a difficult task[2]) but also and especially signs of early injury, including reversible injury.

In this respect, light microscopy has, alas, little to offer. Cell death itself leaves such evanescent traces that we are able to study tissues taken at autopsy—tissues in which practically all cells are dead—and yet call them "normal." Using the microscope, in order to realize that a cell has died, we usually have to wait until it has begun to undergo

From the Department of Pathology, University of Geneva Faculty of Medicine, Geneva, Switzerland.

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Address reprint requests to Dr. Guido Majno, Department of Pathology, University of Massachusetts Medical School, Worcester, MA 01604.

the secondary changes of necrosis. In most tissues this takes 6 to 8 hours.[2] Myocardium does not escape the rule. The consensus is that human myocardial infarcts can be recognized *histologically* only when they are 6 to 12 hours old[3] or possibly 4 to 8 hours.[4] Fine changes in the sarcoplasm of some myocardial fibers have been noticed already after 90 minutes,[4] but only in experimental infarcts, which occurred at predictable sites; such intracellular changes could easily escape notice if the site of the infarct were unknown, as in human material.

Because of these difficulties, a number of other approaches have been explored.[5,6] Histochemistry at the gross and microscopic level has been the most promising,[7,8] but it is too time-consuming to be used as a routine method, it is at the mercy of postmortem autolysis, and simply not applicable where the law requires a 24-hour delay prior to autopsy.[9] Other methods, such as the determination of pH[10] or of electrolytes in samples of fresh tissue[11] are too complicated or unreliable; so is the staining of tissue sections with fuchsin,[12] an empirical, nonspecific, and—in our hands—misleading technic.

Thus, in the 1972 Year Book of Pathology and Clinical Pathology, the situation could be summarized as follows: "Identification of the earliest stages of myocardial ischemia remains a pressing challenge."[13]

In reviewing a series of myocardial infarcts obtained at autopsy in this Institute, we had the good fortune of stumbling across a simple histologic change that makes the diagnosis of early infarcts quite easy, on routine sections. Preliminary notes on this finding have already been published.[5,14]

Materials and Methods

Among the autopsies performed in 1969 and 1970, on patients deceased at the Hôpital Cantonal of Geneva, we selected 46 cases in which death had been ascribed—on clinical grounds—to acute myocardial infarction. All patients (except those who died immediately upon admission) had undergone a complete medical examination at the Hospital, including EKG and at least one determination of serum creatine phosphokinase. The clinical age of the infarct was determined by one or more of the following criteria: a) an episode of precordial pain, resistant to trinitroglycerine; b) gastrointestinal symptoms (pain, nausea, vomiting) without relevant gastrointestinal changes at autopsy; c) a fainting spell or loss of consciousness, leading to irreversible cardiac failure, in the absence of pulmonary embolism, as determined at autopsy; d) a sudden fall of arterial pressure; e) EKG changes typical of a recent infarct; f) increased serum levels of enzymes (CPK, SGOT, LDH), the time-curve being consistent with a recent infarct. Using these clinical criteria, the age of the infarct in our 46 cases may be estimated as follows: 0 to 6 hours, 12 cases; 8 to 12 hours, 10 cases; 24 to 36 hours, 12 cases; 48 to 72 hours, 12 cases.

The autopsy was always complete and was performed within a delay not exceeding 24 hours; whenever the delay was expected to exceed 12 hours the body

was kept at +4 C. For infarcts of less than 24 hours (estimated age) an effort was made to perform the autopsy as early as possible and within a delay shorter than the age of the infarct. When death could be attributed to some other cause than the infarct, the case was eliminated.

The heart was examined by one of us according to the following protocol. After section of the large vessels and gross inspection, the heart was weighed, emptied and submitted to coronary angiography with a barium-gelatin mixture heated to 40 C and injected through the aorta [15] or directly into a coronary artery, at a pressure not exceeding systolic pressure (Ba sulfate, 10/35; gelatin, 1/35; distilled water, 24/35).

The heart was then cut transversely at 10- to 15-mm intervals by means of a simple slicing apparatus; all the slices were laid out, photographed and x-rayed. When the estimated age of the infarct was less than 24 hours, all slices were treated by the histochemical technic of Nachlas and Shnitka for the demonstration of succinic dehydrogenase with nitro blue tetrazolium (NBT)[7] and photographed in color. On the base of the heart, the coronaries were examined by transverse cuts every 10 mm; then the base and all the slices were fixed in buffered formalin. Samples for histology were taken from all infarcted areas (or those suspected to be such) and carefully mapped out on the photographs. When no area of infarction could be identified, either on the fresh tissue or after NBT staining, samples were taken from the entire circumference of the left ventricle. The tissues were embedded in paraffin, sectioned at 5 μ, stained with hematoxylin and eosin, and occasionally by other methods (van Gieson, phosphotungstic acid–hematoxylin, Gomori trichrome).

Results

In studying the more advanced lesions (24 to 72 hours old) we noticed a deformation of the myocardial fibers—best defined as "waviness"—which we could trace back, without exception, to the earliest infarcts, including those cases in which death had been sudden or delayed by 2 to 3 hours. We will first describe this feature, as it appears in hematoxylin and eosin-stained sections.

Definition of the "Wavy Fibers"

The most obvious example of wavy fibers is shown in Figure 1A. Compared with those of normal myocardium nearby (Figure 1B) the abnormal fibers are rhythmically bent *as well as stretched*, and the curves formed by adjacent fibers are, on the whole, in register. However, a closer look shows that there are smaller waves within the waves (Figure 1A, arrows); it is therefore convenient to distinguish waves of several—in fact three—orders.

First-Order Waves

These are the small wiggles formed by single fibers, as just described (Figure 1A, arrows); some are more in the nature of curls, others are angular, as if the fiber had become stiff. Such twisted fibers occur sometimes singly, as a minimal aberration in a patch of otherwise nor-

mal myocardium; sometimes in groups, which therefore appear as if a patch of myocardium had become stretched and "untidy" (Figure 2A and B); and sometimes along waves of second order.

Second-Order Waves

The second-order waves affect bundles of parallel fibers; the period is about 0.3 mm and is fairly constant within a given focus (Figure 1A).

Third-Order Waves

The least common, the third-order waves, occur when a bundle of wavy fibers is, in turn, undulating (Figure 3).

It is self-evident that all the patterns just described refer to myocardial fibers cut longitudinally. If the fibers are cut otherwise, the result is a *banded pattern:* bands of dots (cross sections of thin fibers) alternating with bands of segments (the crests, or the sides, of the waves) (Figure 4A and B); it is therefore still possible to make the diagnosis of "wavy myocardium."

Topography of the Wavy Fibers

The largest and hence the most "typical" patches of wavy myocardium were of second-order waves (Figure 1A). When associated with an advanced infarct, they were usually found at its edge (Figure 5A); in this case they could be either necrotic or not—but in any event they never extended throughout the infarct unless it was a very small one (Figure 5B). Within the infarct itself, the bulk of the tissue was not wavy; its necrotic fibers were usually thinner than normal. We did observe small patches of nonnecrotic wavy fibers which seemed to constitute the entire lesion, in the midst of apparently normal myocardium; we took these to represent miniature early infarcts (indeed we also found older lesions of the same type and size, but definitely made up of necrotic tissue).

The *limit* between normal myocardium and wavy fibers was generally sharp, especially in more advanced lesions in which the wavy fibers had become necrotic and therefore stood out by their brighter eosinophilia (Figures 6 and 7); in a parallel series, one fiber would be straight and normal, the next one would be wavy (Figures 6 and 7). Where straight and wavy fibers met end to end, the transition was equally sharp; at times it was possible to draw a line between the two zones (Figures 8 and 9).

The *subendocardial fibers* were usually spared, presumably because they were supplied by diffusion through the endocardium. Thus, a wavy

area would be separated from the endocardium by a thin layer of straight fibers, 5 to 6 fibers deep (roughly 1 to 12) (Figures 6 and 17). This is the same layer that is well known to survive, temporarily at least, to acute ischemia. There were two interesting exceptions, which confirmed the rule: the subendocardial fibers *did* become wavy a) when the endocardium was covered by a thrombus and b) when it was pathologically thickened. In both cases, normal diffusion from the cavity of the heart was obviously impaired.

As to *subepicardial fibers*, the situation was not so constant; sometimes the waviness stopped short of the epicardial fat (Figure 7), other times it reached it.

Periarteriolar fibers within an area of waviness were sometimes spared (Figures 10 and 11): this suggests that some blood still percolated through the area, but not enough to keep it all alive. It also indicated that diffusion through the wall of the arteriole is enough to sustain several layers of surrounding fibers. Again, in this situation, the limit between straight and wavy areas was clearcut: the change occurred from one fiber to the next.

Cytology of the Wavy Fibers

It is important to realize that *wavy fibers are not necessarily necrotic*. Besides their undulations, the only other major and constant characteristic is their thinness. They appear stretched, even filiform, especially in older lesions (Figure 5); it is instructive to compare their caliber (Figure 1A) with that of surrounding unaffected myocardial fibers (Figure 1B). In advanced stages, the features of coagulation necrosis develop; then the fibers acquire a deep eosinophilia that makes them all the more remarkable. At this point the junction with normal fibers becomes sharper; up to a given intercalated disc the fiber may appear normal and beyond it look "drawn out" (Figure 12).

The *cross striation* was best studied in sections stained with PTAH; along waves the banding was often impossible to recognize, but when visible it was wider than in neighboring straight fibers. All stages of elongation could be found, until the periodicity disappeared altogether (Figure 14). In a few instances, while studying the cross striations under high powers, we saw an intracellular waviness: that is, bundles of undulating fibrils within a myocardial fiber (Figure 13). Since this finding was only occasional, we did not assign it a fourth place in our orders of waves.

The *nuclei* were usually elongated; it was again useful to compare them with those of surrounding unaffected fibers (Figure 1A and B).

In the earliest stages they were simply stretched; later they became pyknotic or disappeared. The *cytoplasm* (apart from the change in periodicity) appeared normal in those lesions that we interpreted as the earliest, but it began to become eosinophilic very soon—exactly how soon we cannot say, but it was commonplace to see some eosinophilia even in the absence of intravascular marginating polymorphs.

Contraction Bands

These bands are a discrete but important sign of cellular disease in early infarcts. They appeared not within the wavy fibers, but in a narrow zone of myocardium between the wavy and the normal (Figures 9 and 17B); when the tissue pattern was such that the myocardial fibers ran straight into an infarcted area, these fibers developed, as a rule, first a few contraction bands, then the waves (Figure 9). These bands correspond to a focal, highly pathologic spasm, whereby adjacent sarcomeres fuse (see discussion); when they involve a large number of sarcomeres, the piling up of cellular material is enough to cause a bulge. We found them only in early infarcts (up to about 6 hours), and either in the proximity of waves or scattered diffusely. In one infarct (clinical age 6 hours) wide contraction bands were aligned in parallel fibers, and the spastic nature of the change was betrayed by the severe deformation of the nucleus (Figure 15), a caricature of the nuclear deformation observed in contracted endothelial cells[16] and in contracted fibroblasts.[17]

Myocardial Fragmentation

When present, myocardial fragmentation spared the wavy fibers; there seemed to be an incompatibility between the two conditions so clearcut that in scanning a slide we could rule out a recent infarct if it showed diffuse fragmentation. When a slide of fragmented myocardium contained a patch of wavy fibers, the contrast between the two was striking (Figure 16A and B). Fine cracks, however, could usually be seen in the wavy fibers in the marginal zone.

Vascular Changes

We are referring herein to changes visible in areas of waviness. The only constant finding was a dilatation and congestion of the fine vessels. This was most obvious in the venules (Figure 2A and B), but a closer look usually revealed that the capillary network was also congested, occasionally to the point of rupture and extravasation of blood. *Edema* was difficult to assess and we disregarded it.

Cellular Infiltration

In two cases of sudden death (Figures 3 and 17) the number of intravascular polymorphs, in and around the wavy areas, seemed normal; counts were not made. At 4 to 6 hours margination, diapedesis and cellular infiltration were under way, and increased thereafter. However, we feel that the timing of polymorph appearance is not yet settled, as will be discussed below.

Discussion

Early in our study of infarcts it dawned upon us that those graceful myocardial waves, that both of us had vaguely noticed many times before, actually conveyed an ominous message: acute myocardial ischemia. They did not appear in other areas of the left ventricle taken from the same hearts; nor did we find them in the vast majority of hearts from our three to four daily autopsies. We will now examine their significance.

Are Wavy Fibers an Artifact?

The question deserves to be asked, because wavy fibers must have been seen by practically all pathologists, year after year, for not much less than a century—and dismissed as insignificant, or possibly as artifacts. We will therefore summarize the arguments that raise them to the rank of pathologic entity.

To function properly, normal myocardial fibers must of course be straight (or curved around natural structures). All fixatives maintain this straight shape.

One possible mechanism of waviness that might be taken into account is *rigor mortis*. If a strip of striated muscle is maintained *in vitro*, under certain conditions, and allowed to contract freely, some of its fibers undergo rigor and shorten, forcing the others to become wavy.[18] The illustrations of Bendall (Plates Ib and III)[18] recall some of our own, except that the wavy fibers are of normal caliber. However, this phenomenon can not be relevant to our study for a number of reasons: it does not account for the relatively rare occurrence of myocardial waviness, for its topographic relation to infarcts and above all for the stretched aspect of its fibers.

Rough handling of the tissue, and especially the use of a blunt knife for sampling, may tend to dissociate the myocardium and to stretch a fiber or two at the edge of the section; but this, too, can be ruled out as a significant source of waviness, at least in our material.

Whole bundles of normal-looking fibers sometimes run a sinuous course, with long shallow curves, perhaps because the last systole was

uneven; a similar pattern can develop where the tissue curled up or was bent. These pseudowaves are easily recognized because they are not made up of stretched fibers.

Waves such as those described in this paper have definitely formed *in vivo* and represent cellular injury because a) they are found in or around all established myocardial infarcts, without exception; b) they sometimes show the classic features of necrosis and c) they tend to spare the subendocardial and periarteriolar zones, thus confirming that ischemia is an essential step in their pathogenesis. The only "artifact" that could conceivably give rise to a differential diagnosistic problem are the small foci of waviness induced by terminal (agonal) circulatory disturbances. We will return to this point later.

Pathogenesis of the Wavy Fibers

In a bundle of straight parallel fibers, if some become thinner and wavy, one is forced to conclude that they have become too long for the bundle. In the heart, a significant elongation can only occur by stretching; and the wavy fibers related to acute ischemia show, indeed, all that is required to conclude that they have been stretched: they are thinner, their nuclei are usually elongated and their periodicity is greater than normal—when not grotesquely stretched. The next step is therefore to explain why these particular fibers have been stretched.

We propose the following sequence of events. A given mass of myocardium becomes acutely ischemic; within it, the fibers will cease to beat; physiologic studies have shown that this occurs within 30 to 60 seconds.[19] Now these immobilized fibers are still attached, at both ends, to fibers that continue to pulsate; hence, *at every systole*, they will be submitted to a powerful tug. It stands to reason that before long —perhaps within minutes, possibly within seconds—they will begin to give way (myocardial fibers have a plasticity well known to physiologists; they have no definite resting length). Soon they will be too long for the stroma that contains them, and they will be forced to develop multiple bends. Local mechanical conditions will determine whether adjacent fibers will bend at random, producing first-order waves, or in synchrony, producing second-order waves.

If this sequence is true, as we believe it is, several other facts have to be explained. First: why does the center of the infarct usually consist of straight fibers?

To understand this, one should visualize a set of live fibers rhythmically pulling at the edge of a recent infarct. Each pull is transmitted, along the fiber, from the live to the paralyzed part, which will tend to

stretch; but farther inwards, toward the center of the infarct, each paralyzed fiber is attached to its neighbors, as well as to the stroma (through the sarcolemma); the mechanical pull is therefore dispersed in all directions, and these distant parts of the fibers are not "drawn out."

A second mechanism, however, contributes to stretch the infarct, when it affects the entire thickness of the myocardium. Within 1 minute after the onset of ischemia, the infarcted portion of the wall begins to bulge outwards at every systole—as a beginning aneurysm—under the effect of intracardiac pressure;[20] slowly the ventricular wall loses its elasticity and gives way. Thus arises, we believe, the peculiar stretched pattern in the center of most infarcts, where the fibers are abnormally thin, straight and rigidly parallel.

Another functional problem that requires analysis is the apparent contradiction between the elongated, *ie,* relaxed state of the wavy fibers, and the common knowledge that death causes muscle to become stiff, *ie,* inextensible (rigor mortis). Muscular physiology offers a simple explanation. In a study of cardiac muscle, Girardier *et al* have shown that anoxia affects electrogenesis far earlier than the store of ATP; that is, as soon as the fiber is asphyxiated, it will cease to beat, but its store of ATP will drop relatively slowly.[3,21-23] Now ATP, in muscular physiology, has a double function; it acts as a contracting substance if it is split, but as a relaxing substance if it is present without being split.[24] In the latter function it has the effect of "lubricating" the actin and myosin filaments so that they can slide over each other, thus allowing the muscle to stretch. This means that the ischemic fibers, though paralyzed, will continue to make enough ATP to remain plastic and let themselves be stretched. By the time that the concentration of ATP becomes low enough to allow rigor mortis, the fiber is already pulled out of shape.

The stiffening of rigor mortis is due to an irreversible chemical bond that locks together the actin and myosin filaments. This happens when the ATP, which keeps the filaments apart, and the pH drop below a critical level.[18] Whether a myocardial infarct can undergo rigor is uncertain. Stretching, to such a degree that the filaments have slid past each other, presumably makes rigor impossible. Hort has found that infarcted areas of rat hearts become incapable of developing rigor within 15 minutes of coronary ligature.[25]

The Contraction Bands

In connection with rigor we should discuss the significance of the

contraction bands, another form of pathologic shortening (Figures 9 and 17). These eosinophilic bands are a useful adjunct in the diagnosis of early myocardial ischemia. By electron microscopy they correspond to dense filamentous areas, in which several sarcomeres are fused, as if filaments from adjacent sarcomeres had slid together.[26–28] The underlying mechanism is not clear. In relation to experimental infarcts, they form *around* areas of total ischemia (within 90 to 120 minutes), whereas after temporary occlusion they form *throughout* the affected area (40 minutes' occlusion + 20 minutes' reflow).[4,29] It has been suggested that cell death is a prerequisite, and that they are probably produced by the contractile force of surrounding viable fibers acting on irreversibly injured cells.[19,26] It seems more likely that the sarcomeres flow together by an *active*, intracellular spasm (*spasm bands* would be a more appropriate name, for the contraction involved is highly abnormal). That the myocardial fibers must have died for contraction bands to develop is also questionable. Vitali-Mazza *et al* caused left ventricular failure in rabbits by means of acute aortic stenosis, and found typical contraction bands within 45 minutes.[27] Henson *et al* found them in the hearts of 13 patients who were undergoing open heart surgery and died on the operating table.[30] This suggests that they represent a fairly early type of injury; indeed we found them in a case of sudden death by infarction (Figure 17).

From the published data, and from our own, it would seem that contraction bands develop in areas of "twilight blood flow." Physiologic studies have shown that they can form also *in vitro*, in living myocardial fibers, when they are pulling without an opposing force;[31] our observations fit this, too, for we found contraction bands *between* the normal and the wavy myocardium (Figures 9 and 17), where the circulation is faltering, and where the surviving part of the fiber is pulling against a weak, and weakening, resistance.

To sum up, the presence and distribution of the contraction bands fit very well with the ischemic origin of the wavy fibers.

On the "Loss of Striation"

There is a pathologic lore whereby necrotic myocardial fibers lose their striation. Sometimes they do; yet all of us have known the frustration of finding beautiful striations in the very middle of an infarct. What is really happening?

Striations seem to be quite resistant to necrosis; however, when the fibers are stretched, the striations are literally pulled apart and destroyed. This is easy to see in wavy fibers; the striations spread out,

and as the fibers become thinner and thinner, they break up into scattered granules without any trace of order. Hence it is true that necrotic myocardial fibers *can* lose their striation fairly early in the process of necrosis—*if they are stretched.* But in the very middle of the infarct, where the stretching is not as drastic, the striations will have a greater chance of persisting.

Are the Wavy Fibers Irreversibly Injured?

A final answer to this question must wait for experimental studies. However, it can be said that the phenomenon of waviness develops very quickly, probably in a matter of minutes or even less,[32] that is, before the cell can be called dead or even irreversibly injured. The fact that it presumably still synthesizes ATP lends support to this hypothesis. Studies on the dog have shown that the myocardium can recover without apparent damage from a period of ischemia of up to 18 minutes.[33] The results of different authors are somewhat at variance, perhaps because of species differences;[33] but according to a recent study of temporary coronary occlusion in dogs, the infarcted area resumed beating after a period of ischemia as long as *1 hour.*[34] It is therefore quite possible that the wavy fibers, up to a point, may remain able to pull themselves back into their normal shape and length. Those that have reached the stage of attracting polymorphs are probably dead.

The Diagnostic Use of Wavy Fibers

The first step in our work was to show that wavy fibers are found in and around all infarcts; the next must be to prove that they are present also *before* the established infarct—that they are the first histologically visible effect of acute myocardial ischemia. Definitive support for this statement will be found in a forth coming paper describing the histology of experimental infarcts in the rat.[32] With human material, absolute proof can never be given; however, in this Institute, we have been using the criterion of wavy fibers ever since our first observations some 4000 autopsies ago, and the consistency with the clinical findings has been as good as could be hoped for. A typical example (Figure 17), from a case of sudden death, shows most of the features that we regard as "classic": waves that spare a subendocardial layer and contraction bands between the two (missing are the dilated vessels).

In fact, we now face a paradox: wavy fibers form so fast that we are practically unable to grade infarcts between 0 and approximately 6 hours, at which time polymorph infitration is obvious. This is not critical, because the important point is usually to establish whether an

early infarct is present or not. In our material, contraction bands, and some increase of eosinophilia, seemed to develop very fast—*perhaps* less than an hour (Figure 17). Experimentation on animals larger than rats and rabbits should give clues to a better histopathologic timing.

In routine cases during the past 2 years, we have gained the impression that *margination* appears much earlier than the 6 hours usually mentioned since the paper of Lodge-Patch [35]—perhaps as early as 1 hour; in experimental infarcts in the dog, the first neutrophils have been seen to appear after 1 to 2 hours [36] and 2 to 4 hours.[8] This important diagnostic problem must also wait for further experimental studies. So far it could not be reliably solved for a number of reasons: lack of histologic criteria for diagnosing a myocardial infarct more recent than 6 hours, poor correlation between clinical symptoms and anatomical changes, and the patchiness of myocardial infarcts.

The data at hand are sufficient to conclude that "waves" are a safe and highly sensitive criterion for the diagnosis of acute ischemia. Now this very sensitivity raises a question. If it is true that minutes of circulatory failure are enough to make the fibers wavy, *then what is going to happen during the agonal period?* Are there not going to be some false positives that are not real clinically relevant infarcts, but just terminal events?

In practice, the danger is not significant. However, the following qualifications must be kept in mind: a) very small patches of waviness, affecting groups of a few fibers, can be found in many tissue sections; they are not associated with margination of polymorphs. They are so small (usually a millimeter or less in diameter) that their lack of clinical significance is patent. We consider them as terminal. A rough estimation is that we find one or two in most histologic sections of the left ventricle. b) There must be rare intermediate cases, in which terminal circulatory failure does cause the beginning of an infarct, which did not have the time to manifest itself clinically. These problems are now under study; suffice it to mention here that what counts is the *extent* of the waviness, for this is what determines the clinical significance of the ischemic area. The clinician is not interested in learning that autopsy showed a few microscopic foci of agonal waviness, no more than he cares about myocardial fragmentation. He might be more interested in learning that if his patient had survived, he would have developed a sizable infarct.

Relation of Wavy Fibers to Myocardial Fragmentation

Though the significance of myocardial fragmentation is still obscure,

we found it very useful at an empirical level: for there seems to be a relationship of mutual exclusion between fragmentation and wavy fibers (Figure 16). In our material, even when fragmentation is severe and diffuse, it will spare the wavy areas. At most, fine cracks may appear; but the *spacing* of the segments, typical of fragmentation, we have never seen (with two dubious exceptions). Hence we have come to accept that *if an area is fragmented, it does not contain a recent infarct.* The same conclusion has been reached by Hort.[37] The reason is probably simple: fragmentation is related, in some way, to a contraction or a spasm of the broken fibers; it therefore implies that the fibers must have retained, up to the very last, some capacity to contract. Wavy fibers are paralyzed by definition; as such they may "break," but the segments can not actually pull away from each other.

Earlier Observations of the Wavy Fibers

We were not the first to observe the wavy fibers, or to photograph them. In 1926, a German author, H. Willer, published a paper on myocardial fragmentation.[38] In the course of this study he had noticed that some hearts contained patches of wavy fibers that did not seem to be artifacts. He speculated, like us, that the fibers in question had become too long for their surroundings; and reasoned as follows: during agony, a bundle of fibers might cease to beat; if the fibers surrounding it then contract, the paralyzed bundle will be cramped into a shorter space and forced into a corkscrew shape. Thus Dr. Willer came very close to stealing the wind from our sails; his explanation is the very same that is now given for the waviness of rigor mortis *in vitro*, as we mentioned earlier. And his two figures are very similar to ours, except that their legends begin with a Latin name: *Undatio myocardii.*

There are hints of waves even in Mallory's classic work on myocardial infarction,[39] notably in his Figure 8 showing a 96-hour infarct. Sommers and Jennings,[4] in 1964, published an excellent illustration of wavy fibers (their Figure 9); they commented very appropriately on the stretching, but did not mention the waviness (see also Figure 1 of Jennings *et al*[19]). Other waves appear in a figure published by Jørgensen *et al*,[40] showing a 4-hour experimental infarct (their Figure 14), and in textbook illustrations such as those of Gould[41] and Hudson.[42] Hort, in 1965, published a study of myocardial infarcts in 400 rats and 1 man.[25] He measured the length of the sarcomeres and found a significant elongation in infarcts; in the rat, within 14 minutes, the average was 1.94 μ against 1.54 μ for the control area; in the human heart, the length became 2.38 μ against 1.68 μ. The method is far too cumbersome for diagnostic purposes. We should mention here that, in our material, the typical wavy

fibers have been stretched to such an extent that the period is no longer recognizable; perhaps this is the reason for which Hort does not mention them.

One cannot help but wonder how a lesion as obvious as the one discussed in this paper could have escaped attention for so long. It is true that there is no significant precedent of a wavy pattern implying injury. Quite to the contrary—many normal nerves look wavy. Also, the earliest myocardial waves are not accompanied by any extracellular changes such as we are accustomed to associate with injury, and this may have helped to dismiss them. But we believe that there is a deeper reason, unrelated to the practice of pathology. There is something beautiful about wavy patterns; they look like an improvement over stiff, parallel lines. In everyday life, judging from current standards, wavy hair is supposed to be more elegant than straight hair. Wavy fibers just looked too beautiful to be called sick.

Conclusions

The histologic diagnosis of early myocardial infarcts is no longer a challenge. Using waviness as a criterion, it can be made on routine sections; even 24-hour autolysis does not affect it. In acquiring personal experience with the method, the following hints may be useful: a) Whenever in doubt as to the significance of a wavy pattern, the aspect of the fibers is decisive; they must show the features of stretching. b) It is very instructive to compare the caliber of wavy fibers with that of straight fibers nearby. c) Primary waves (*ie*, the wiggles along individual fibers) are definite signs of stretching, and easy to find. d) To confirm the significance of a large wavy area: see how it behaves beneath the endocardium, and around arterioles. It should spare a layer of a few fibers. e) With transverse cross sections of fibers giving doubtful pattern: rather than wasting time on it, look nearby. If the infarct is of significant size, its fibers are bound to be cut longitudinally in some other part. f) Wavy fibers on the edge of the section are not likely to be sampling artifacts: they rather mean that the sample was taken in the neighborhood of an infarct. g) Agonal waves are limited to small patches, and h) Fragmented areas are not infarcted.

The next major problem that remains to be solved is gross diagnosis, for we still do not know exactly where to take the samples for histology on the fresh or fixed heart. The NBT method is of no help for human infarcts more recent than 6 to 8 hours.[7,9] When there has been time antemortem for an EKG, that may help. Otherwise we proceed blindly, cut the heart transversely in slices 10 to 15 mm thick, and sample the

third or fourth slice; *zones that seem slightly "hyperemic" we regard as suspect.* On fresh or fixed slices, placed under water and studied with the dissecting lens, wavy fibers are not distinctly visible. They do stand out fairly well if india ink (used as a negative stain) is rubbed onto the surface of a fixed, smoothly cut slice. However, this takes so much time that where adequate technical help is available, it is simpler to multiply the number of blocks.

The purpose of this paper was to introduce the concept of wavy fibers, and to illustrate their major light microscopic features. A forthcoming paper[32] will show that they can be produced experimentally, and perhaps within the time of one powerful systole. Another forthcoming study on right and left ventricles taken from 200 consecutive autopsies[42] will provide statistical figures and illustrate the morphology of those wavy patterns that are *not* significant for the diagnosis of acute myocardial infarction.

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[*Illustrations follow*]

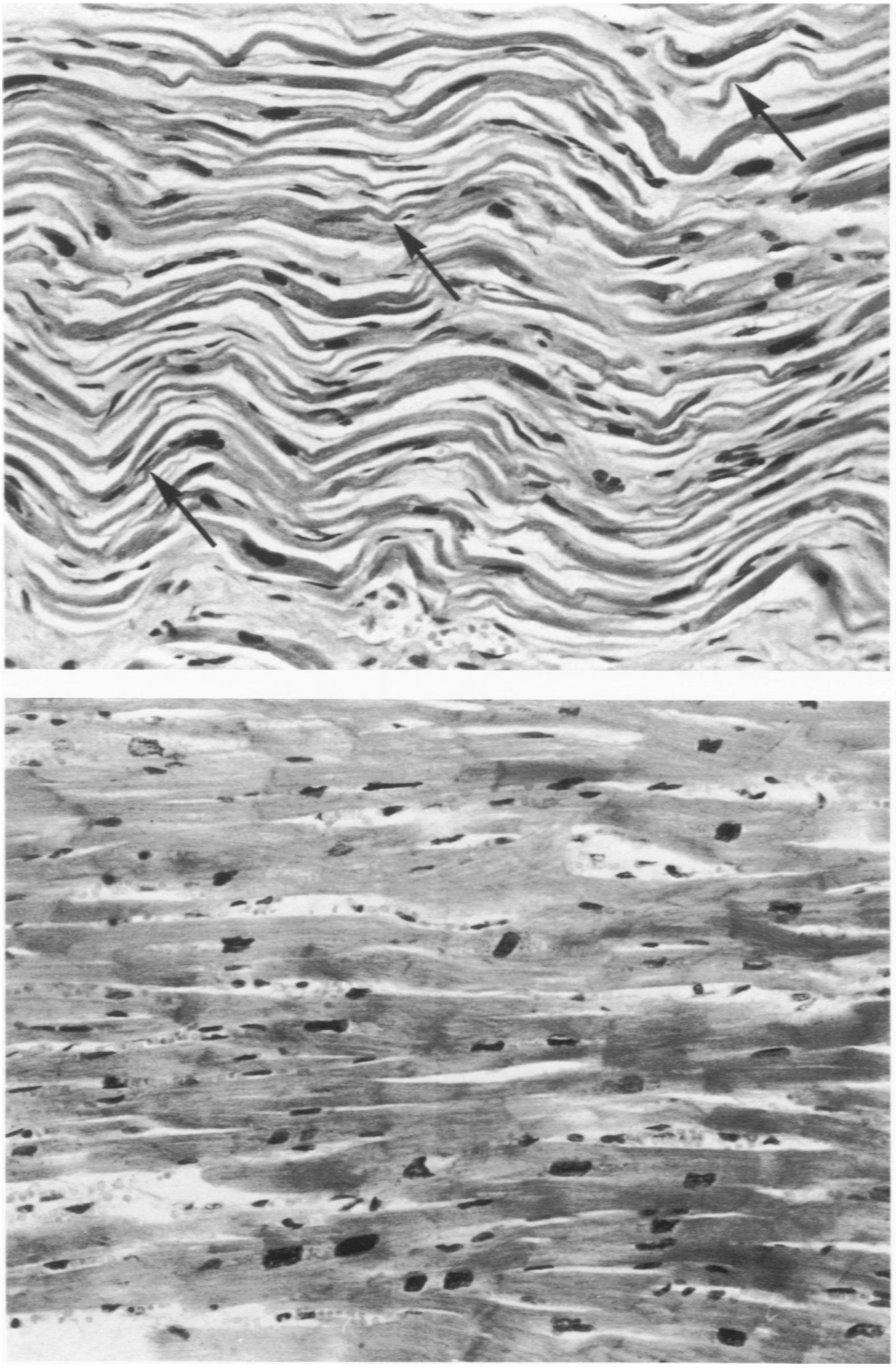

Fig 1A—Typical second-order waves. Clinical age of infarct, 12 hours. *Arrows* point to first-order waves (independent waves of single fibers). Note features of stretching, especially by comparison with (**B**), normal myocardium nearby. Polymorph infiltration was still scanty (H&E, **A,** × 250; **B,** × 250).

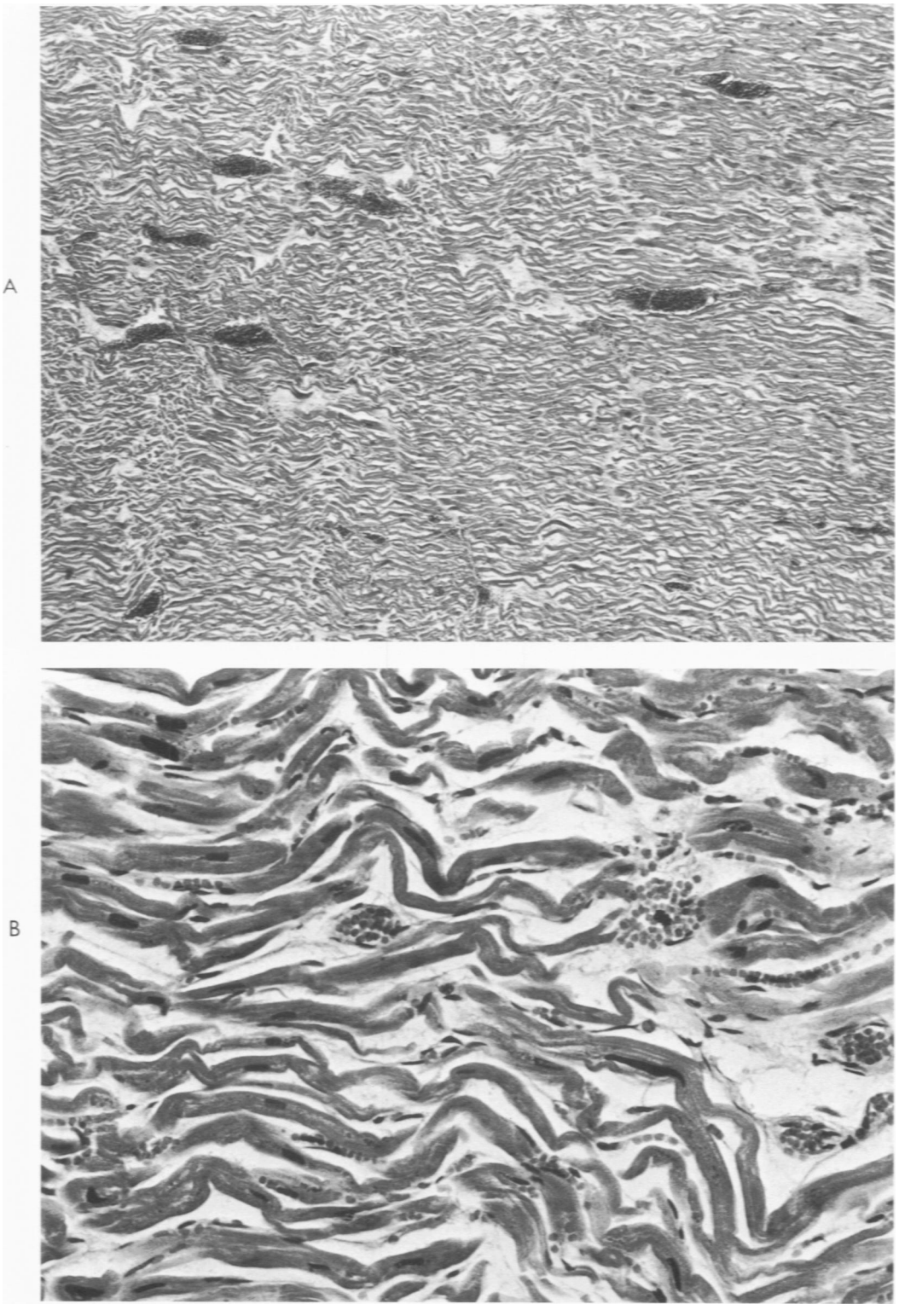

Fig 2A—Area of stretched, wavy fibers and dilated vessels. Clinical age of infarct: 10 hours. Waves are mostly random (first order) with hints of parallel waving at left (second order). **B**—Detail. Note congestion, and typical first-order waves. Polymorph infiltration was scanty (H&E, **A**, × 45; **B**, × 300).

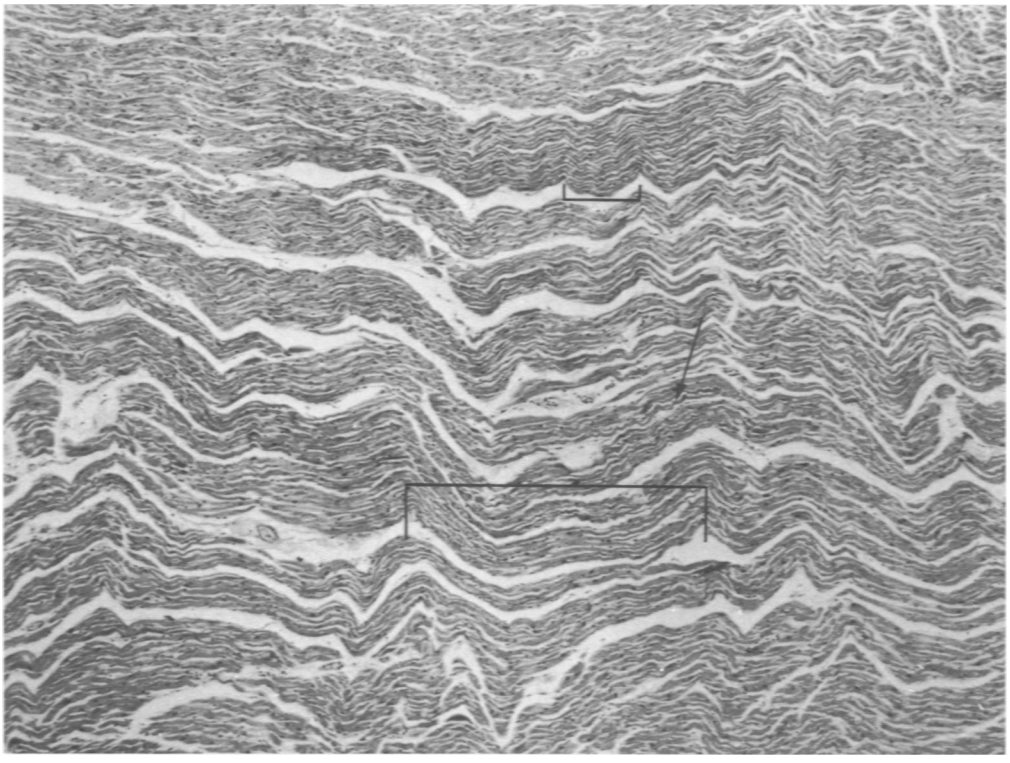

Fig 3—Three orders of waves illustrated in a case of sudden death; this zone was grossly somewhat darker. *Arrow:* first order; *short line:* second order; *long line:* third order. Subedocardial zone was spared. Congestion was obvious in adjacent areas. No polymorph infiltration (H&E, × 50).

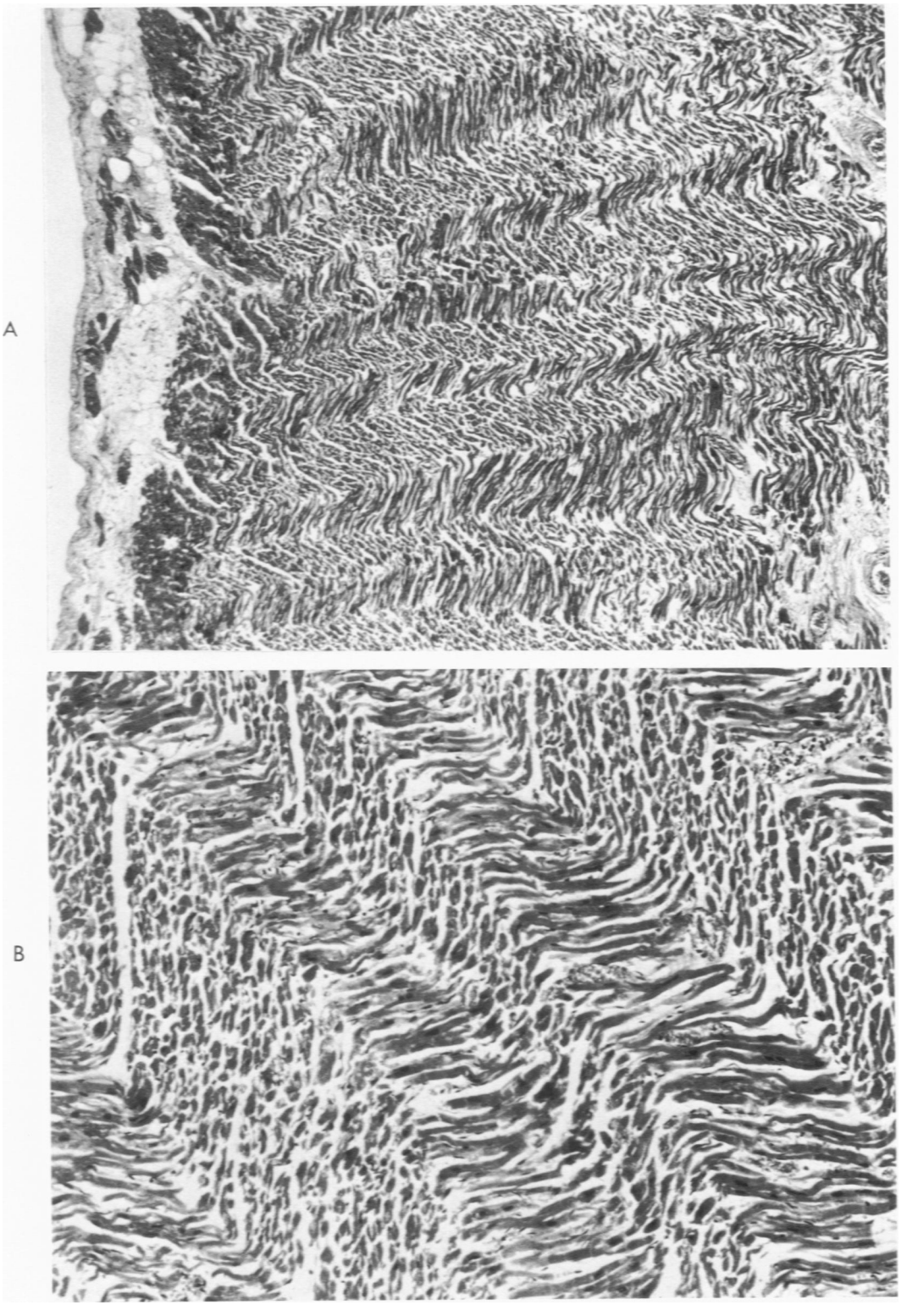

Fig 4—Pattern resulting when wavy fibers are not cut lengthwise. In **A**, subepicardial fibers may not be waving. Clinical age of infarct: 12 hours. Polymorph infiltration was moderate (H&E, **A**, × 50; **B**, × 125).

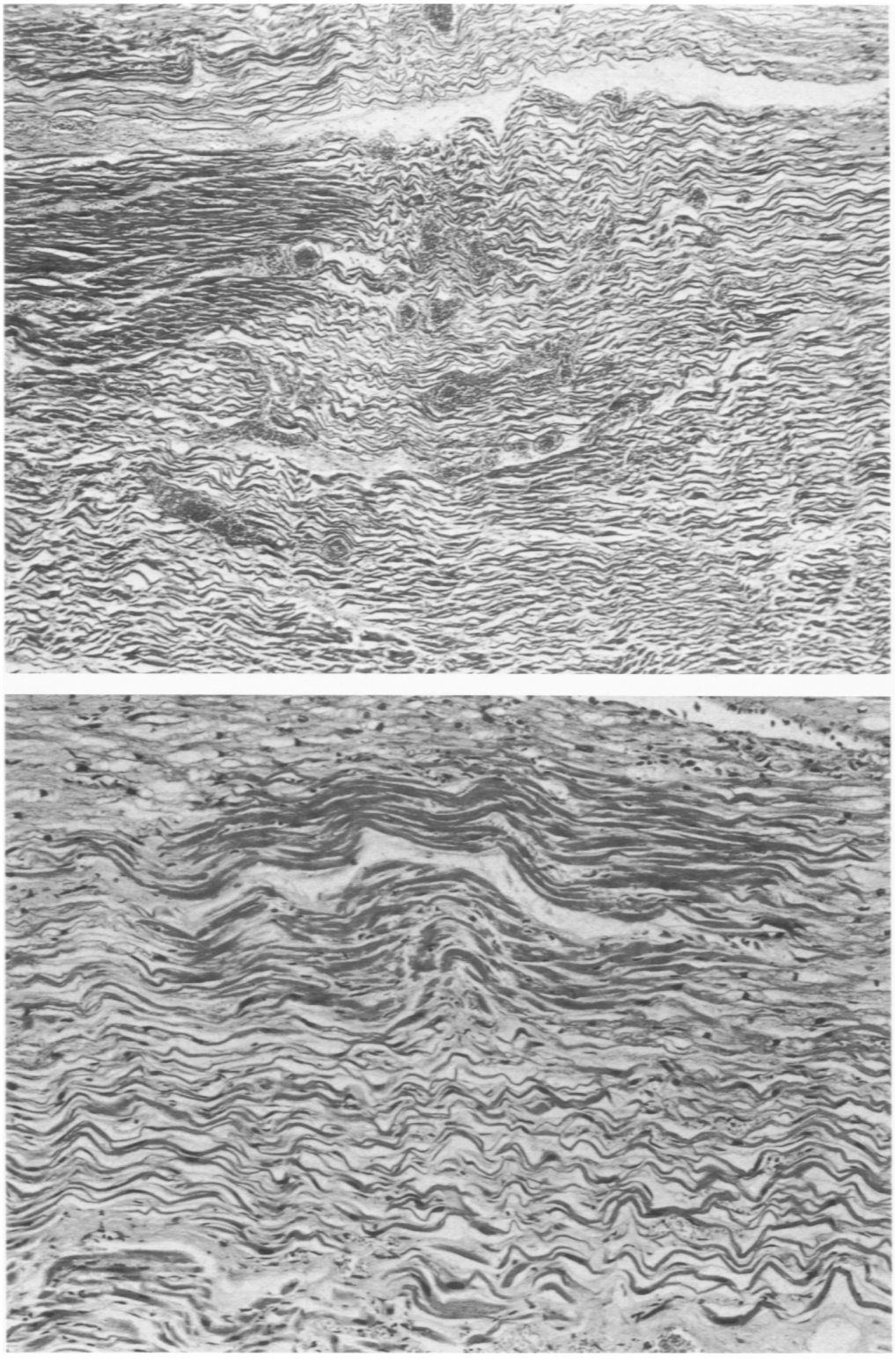

Fig 5A—Wavy fibers at the edge of an obvious infarct (top left). Clinical age: 12 hours. Since this is probably too short for such advanced coagulation necrosis to develop, the infarct must have been silent for some time before symptoms appeared. Polymorph infiltration scanty (the dots in infarct at top left are red blood cells). Note congestion (H&E, × 110). **B**—Same case. Small focus of obvious infarction, indicated by loss of nuclei and coagulation necrosis. Small infarcts such as this one may be constituted entirely of wavy fibers. Polymorph infiltration scanty (H&E, × 115).

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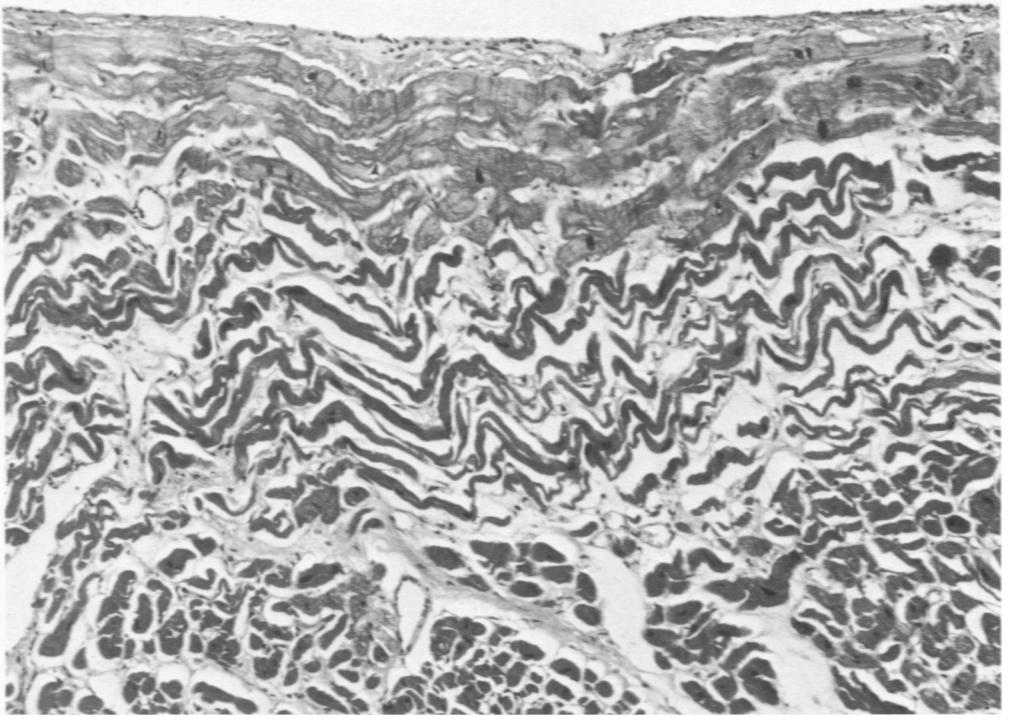

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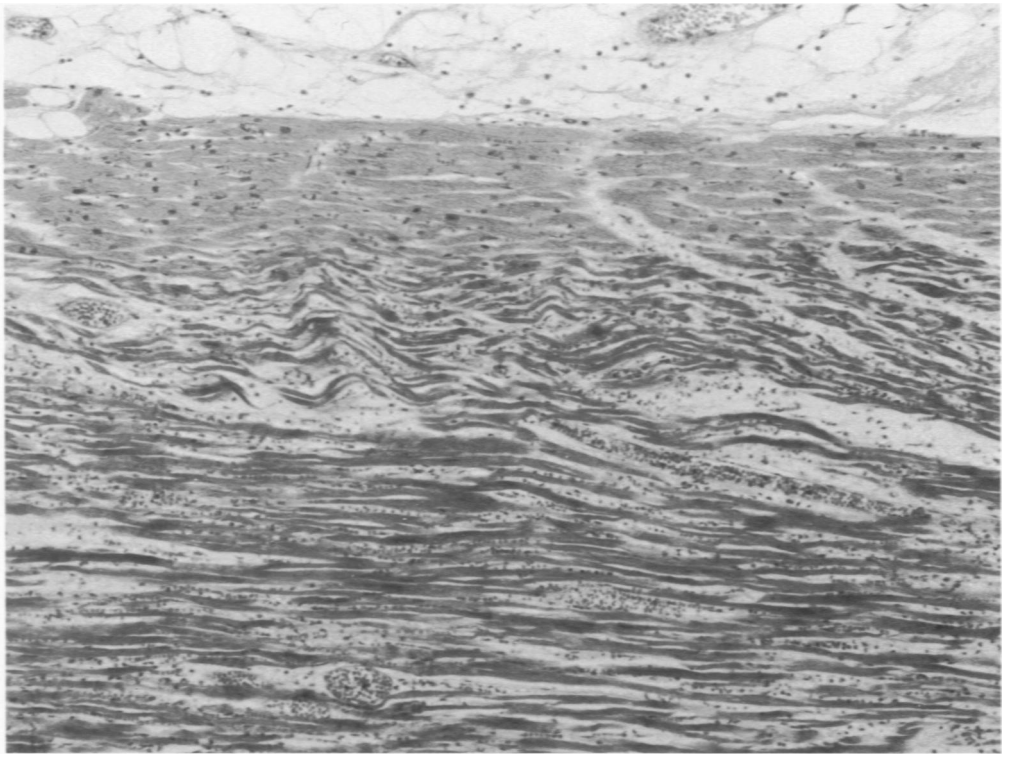
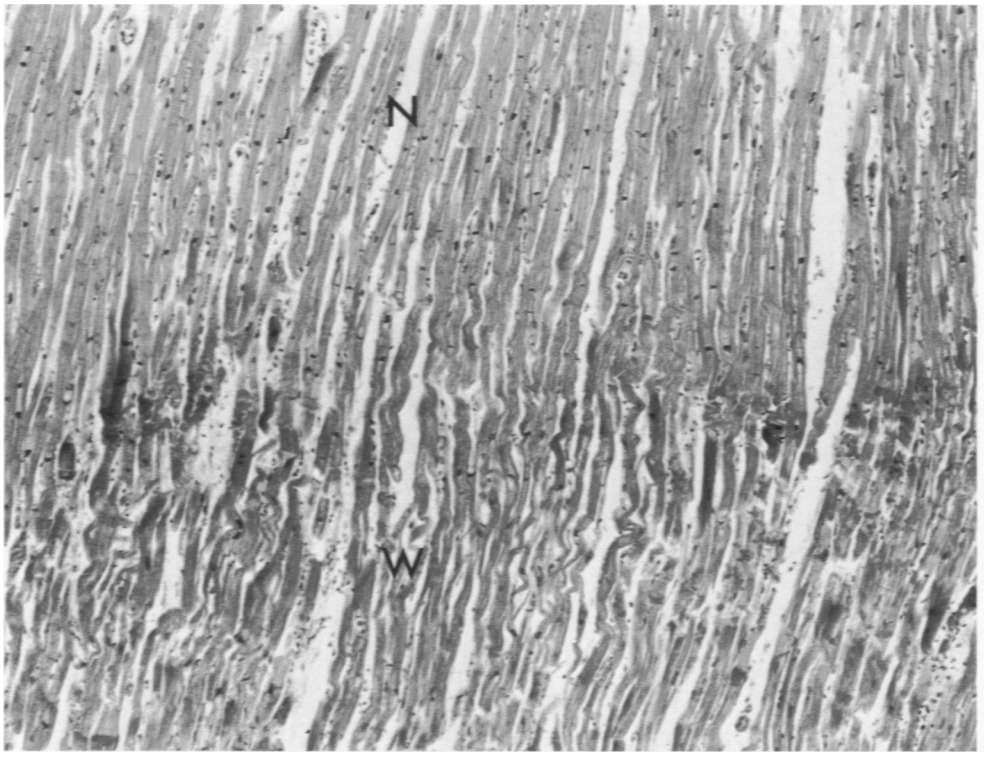


Fig 6—Relative preservation of the subendocardial fibers in an area of waviness. Clinical history: sudden death after 12 hours of chest pain. The deeper fibers are very eosinophilic, with first and second order waves. In this case the subendocardial fibers are also beginning to suffer (swelling, beginning waviness) (H&E, × 115). **Fig 7**—A common pattern. Three layers of fibers at the periphery of an infarct: normal subepicardial straight fibers; wavy fibers; and again straight fibers toward the center of the infarct. Clinical age: 48 hours. Polymorph infiltration extensive. Note that by this time the wavy fibers have become necrotic (H&E, × 115).



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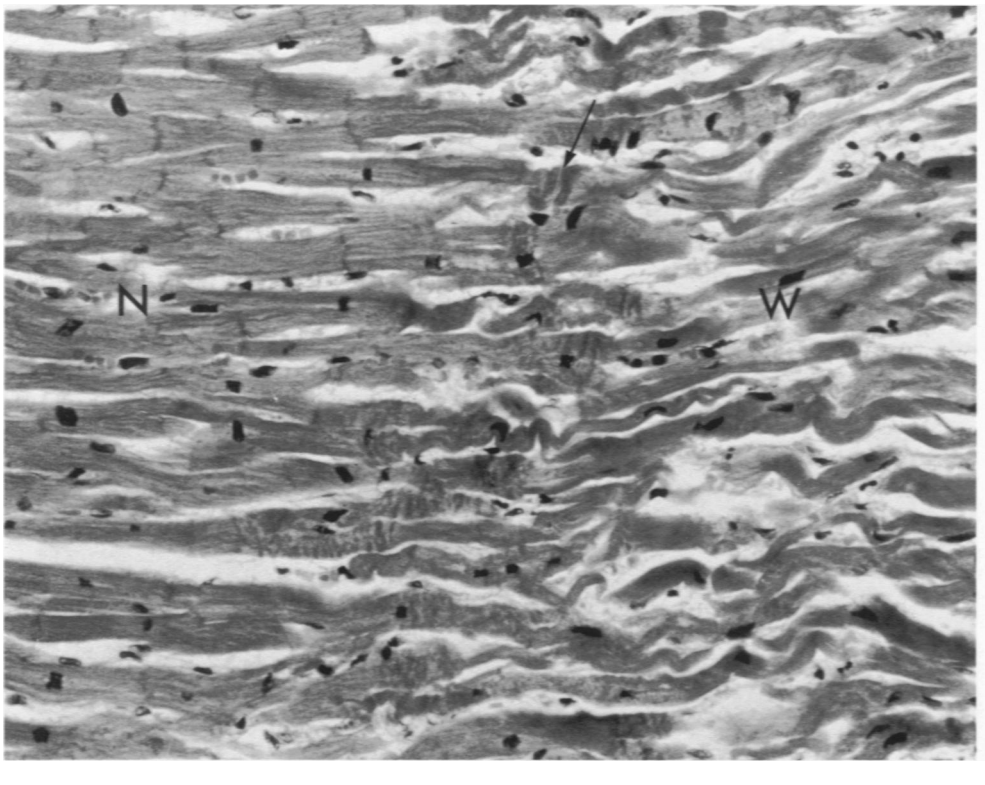

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Fig 8—Edge of a recent infarct: normal fibers (*N*), to be visualized as rythmically pulling at the paralyzed fibers, which become thinner and wavy (*W*). Clinical age: "36 hours" (H&E, × 115). **Fig 9**—Edge of another recent infarct (clinical age: 12 hours). *Arrows* point to contraction bands, which developed between the normal and the stretched areas. Polymorphs are absent from this particular field, but some were present nearby (H&E, × 280).

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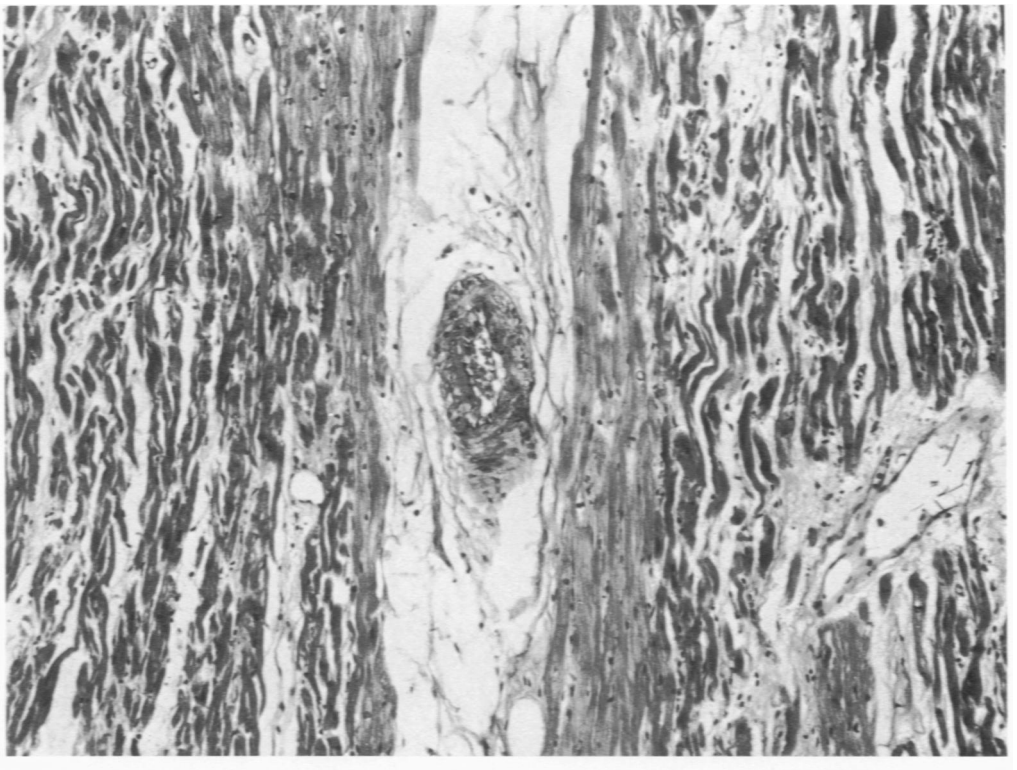

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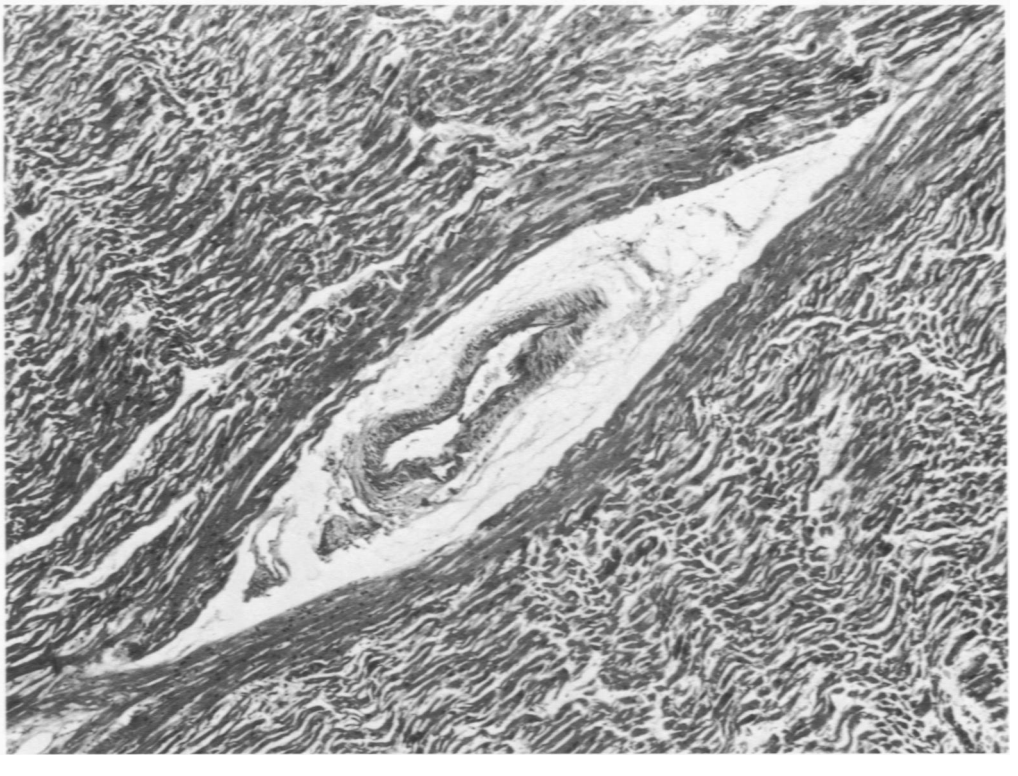
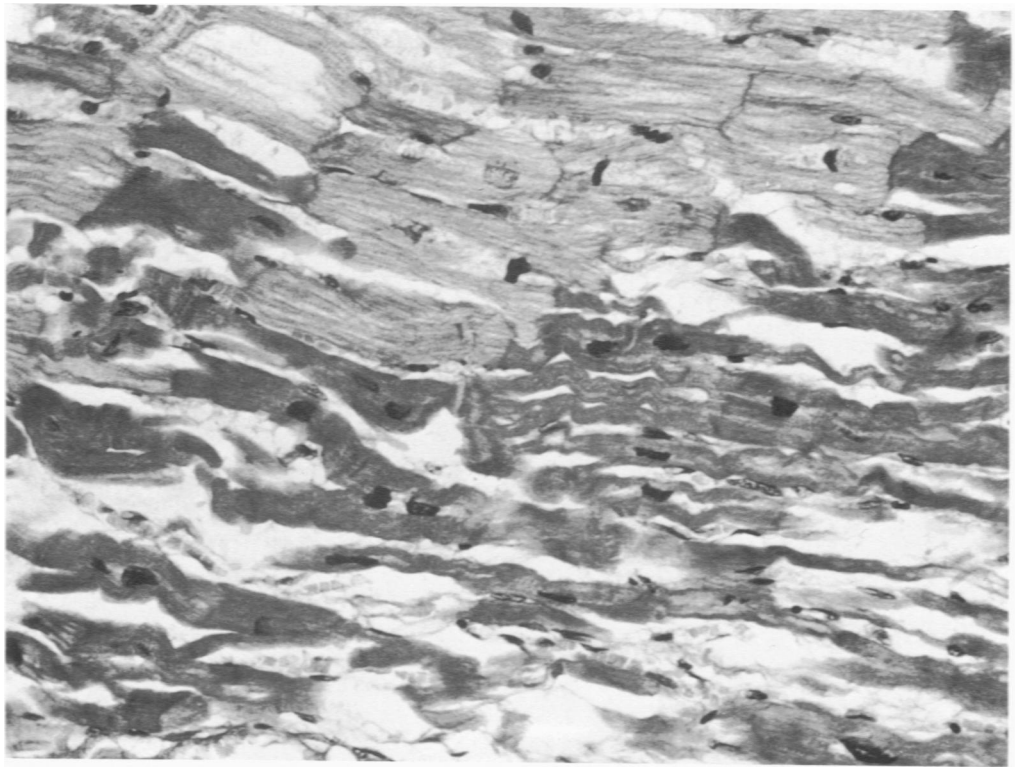


Figs 10 and 11—Preservation of periarteriolar fibers in wavy areas. **10**—Obivous infarcted area, clinical age 24 hours (H&E, × 100). **11**—Clinical age of this infarct was 12 hours. Polymorph infiltration in other areas was definite (H&E, × 45).



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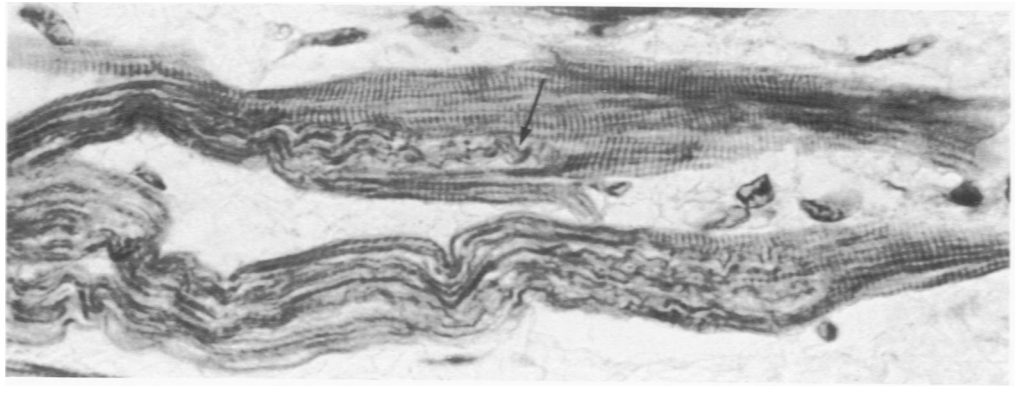

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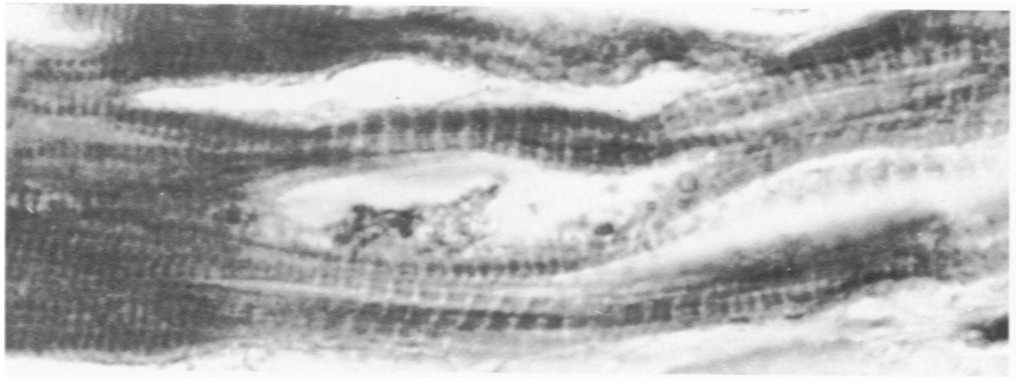

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Fig 12—Limit between live tissue and stretched, wavy fibers, obviously dead and coagulated, in an infarct of clinical age 12 hours. The live fibers are somewhat swollen, making the contrast even more striking. There was some polymorph infiltration nearby (H&E, × 300). **Fig 13**—Intracellular waves, presumably due to stretching of fibrillar bundles (*arrow*). Clinical age of infarct 2 hours (Gomori trichrome, × 800). **Fig 14**—Typical image of stretched fiber, at the point where it is "pulled out". Note lengthened period and beginning waviness (PTAH, × 1900).

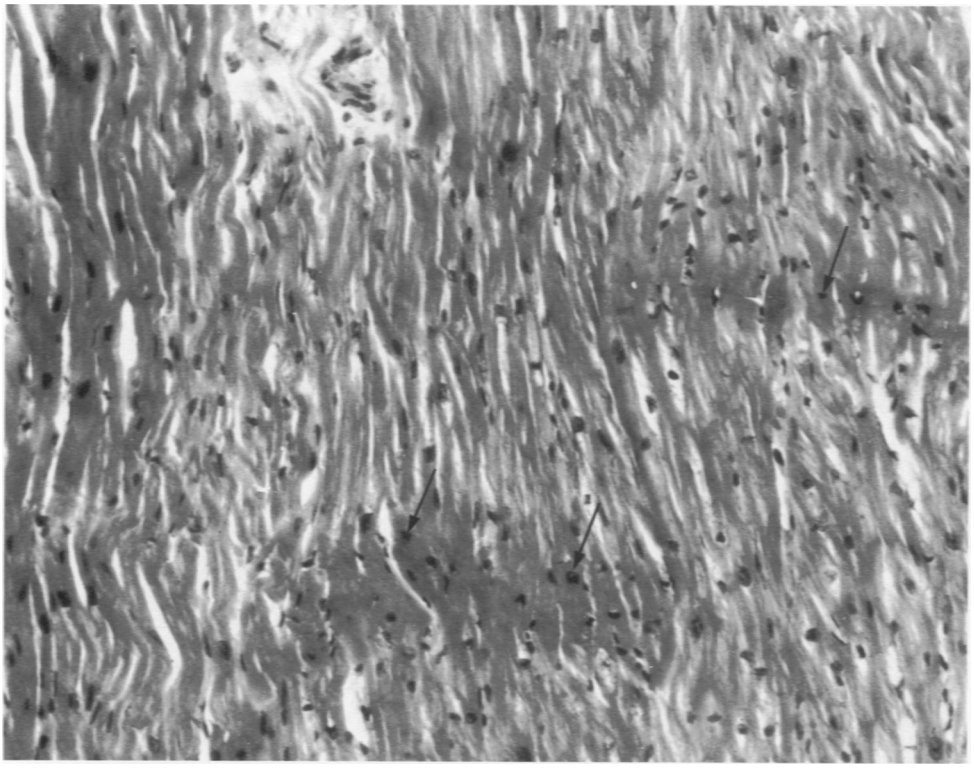

Fig 15—Another effect of acute ischemia: an abnormal spasm in groups of adjacent fibers, giving rise to wide contraction bands. The spasm is betrayed by the deeper eosinophilia and by the deformation of the nuclei (*arrows*). Clinical age of infarct: 6 hours (H&E, × 160).

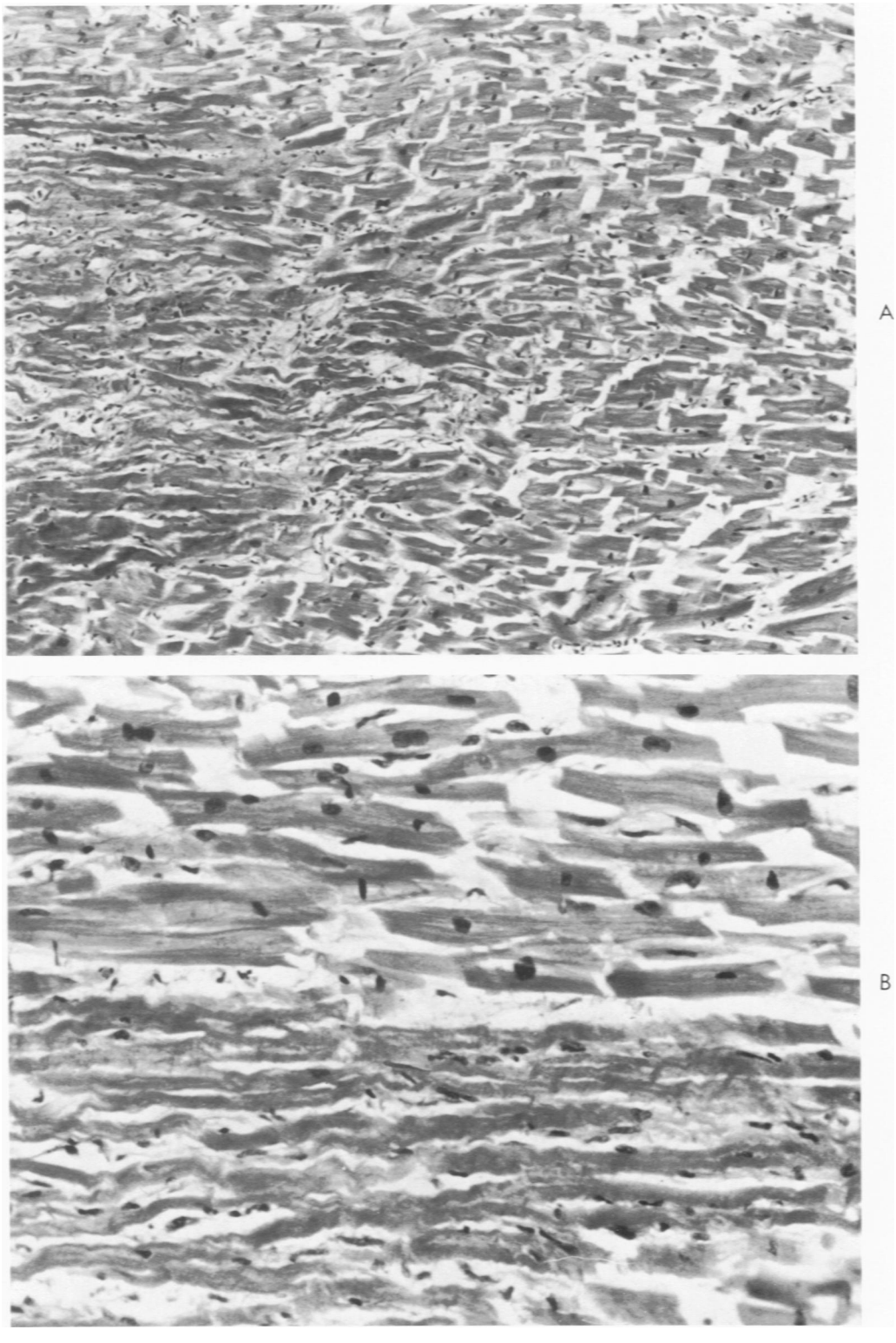

Fig 16—Demonstrating that fragmentation spares the wavy areas. Clinical age of this infarct was 24 hours (H&E, **A,** × 120; **B,** × 280).

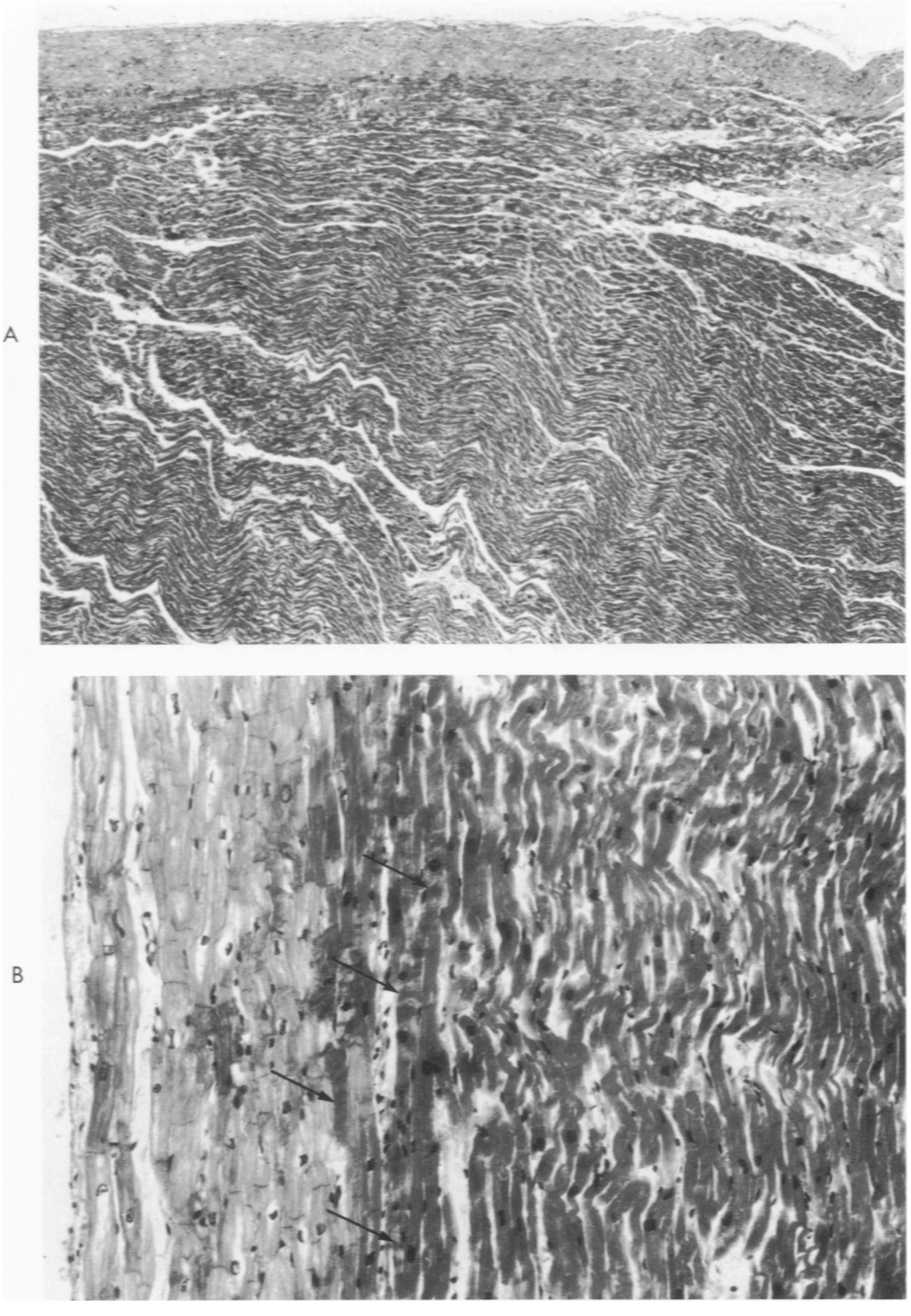

Fig 17—Typical findings in a case of sudden death (man age 59, with a history of repetitive myocardial infarction; sudden collapse at work; resuscitation attempts failed at hospital after somewhat over 1 hour). Low-power view (**A**) shows second order waves, sparing a subendocardial layer. In detail (**B**) note contraction bands (*arrows*) between the living and the wavy areas (H&E, **A**, × 40; **B**, × 100).